

A systematic review and meta-analysis of randomized controlled trials exploring the role of inter-individual variability on the effect of flavanols on insulin and HOMA-IR

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Introduction	Methods							
 Meta-analyses of randomised controlled trials (RCTs) report that polyphenol-rich diets can modulate a range of cardiometabolic biomarkers (1, 2). specifically – flavonol, flavanol, anthocyanin and ellagitannins (3). Inter-individual factors (e.g. age, BMI, ethnicity) may contribute toward the variability in the response to the bioactive. Scope of the Review 1. To assess the effect of flavanols from cocoa, apple and tea on fasting insulin and HOMA-IR 2. To explore the role of inter-individual variability 	 PubMed & Web of Science were searched from inception to October 2017 (PROSPERO reg. CRD42016033878). Estimation of effect of flavanols supplementation on insulin and HOMA-IR using a random effects meta-analysis model reported as standardised difference in mean (SDM) and 95%CI. Multivariate meta-regression: impact of baseline BMI, gender, age, & study location - the standardised coefficient β was reported, alongside 95% CI Evaluation of risk of bias with the Cochrane Collaboration tool modified to include source of funding, baseline comparability. 							
Results								

- 1409 studies screened → 31 RCTs were included reporting on insulin (n=1792); 21 RCTs reporting on HOMA-IR (n=1152).
- Study duration ranged from 2 to 26 weeks and flavanols' doses ranged from 88 to 1344 mg/day.
- Studies followed most often a parallel design; insulin (n=21), HOMA-IR (n=14), with some cross-over studies; insulin (n=10), HOMA-IR (n=7)
- Sample size varied from 23 to 104 for parallel design studies, and 12 to 69 for cross-over design studies.
- 37 RCTs were of moderate risk of bias while 15 were of high risk
- Low heterogeneity between studies (insulin I²=0%, p=0.98, HOMA-IR I²=5.9%, p=0.38) but evidence of potential publication bias (HOMA-IR p=0.000, insulin p=0.005).
- Flavanol-rich interventions decreased both insulin (SDM 0.25, 95%CI -0.33; -0.16, Fig1A) and HOMA-IR (SDM -0.26;

Study name	Sample size		Time		Statistics for	each study		5DM and 94% CI			
	treated	control	point SDM (weeks)	\$204	96 % CI		p-Value		Kalati weigi		
Pukine, 2008 b	60	60	*	-0.143	-0.502	0.215	0.435		6.4		
Fukine, 2008 a	60	60	8	-0.297	-0.636	0.063	0.106		6.4		
Ryw, 2006	55	55	4	-0.099	-0.475	0.275	0.605		5.9		
Mielgo-Ayuse, 2014	59	59	12	-0.000	-0.444	0.444	1.000		4.3		
Hsu, 2008	41	57	12	-0.175	-0.620	0.271	0.442		4.3		
Chen, 2015	39	38	12	-0.058	-0.505	0.389	0.798		4.3		
Belm, 2014 a	38	59	12	-0.110	-0.557	0.397	0.630		4.3		
Lin, 2014	39	38	36	-0.188	-0.635	0.360	0.412		4.3		
Hussain, 2017	40	40	12	-0.629	-1.078	-0.180	0.006		4.2		
Behn, 2014 b	37	59	26	-0.087	-0.537	0.363	0.705		4.2		
Dewer, 2015	35	35	4	-0.339	-0.811	0.133	0.139		3.9		
Hen, 2013	35	53	36	-0.000	-0.476	0.476	1.000		3.8		
Nickels-Richardson, 2014 e	50	50	18	-0.001	-0.507	0.506	0.998		3.4		
Nickels-Richardson, 2014 a	50	50	6	-0.007	-0.515	0.499	0.979		3.4		
Nickels-Richardson, 2014 h	50	50	12	-0.012	-0.518	0.494	0.963		3.4		
Martrojacevo, 2015 a	50	50	8	-0.194	-0.701	0.304	0.454		3.4		
Mastroiaceve, 2015 b	50	50	8	-0.233	-0.741	0.275	0.349		3.4		
Desideri, 2002 b	50	50	8	-0.360	-0.871	0.150	0.166		3.3		
Desideri, 2002 a	50	50	8	-0.622	-1.141	-0.304	0.019		3.2		
Bogdanski, 2012	28	28	15	-0.567	-1.104	-0.053	0.038		3.0		
Almonsawi, 2013 a	21	21	4	-0.361	-0.971	0.249	0.246		2.4		
Barn, 2010 a	13	5	8	-0.402	-1.006	0.212	0.200		2.3		
Almoosawi, 2013 b	21	21	4	-0.617	-1.236	0.002	0.053		2.3		
Grassi, 2005	20	20	2	-0.627	-1.242	0.008	0.013		2.2		
Grassi, 2008	19	19	2	-0.901	-1.462	-0.340	0.018		2.0		
Stendell-Hollis, 2010	19	14	26	-0.671	-1.380	0.038	0.064		1.7		
Maller, 2010	12	12	8	-0.195	-0.997	0.607	0.634		1.4		
Davison, 2008	12	11	12	-1.064	-1.938	-0.390	0.017		1.3		
Barn, 2010 b	12	5	8	-1.512	-2.596	-0.427	0.006		0.7		
Random overa	ll effec	ct		-0.268	-0.364	-0.372	0.000				

95%CI -0.36, -0.16, Fig1B).

Multivariate meta-regression:

- 1. No discernible effect of age, gender, baseline BMI, study location on the insulin response to flavanols.
- 2. Baseline BMI (overweight but not obese vs lean, β -1.07; 95%CI: -2.03, -0.08; p=0.03) and study location (Asia versus other sites β 0.94; 95%CI: 0.03,1.84; p=0.04) influenced HOMA-IR response to flavanols.

Conclusions

- Flavanols from tea, apple and cocoa promote small but beneficial changes on insulin and HOMA-IR and may contribute to prevent cardiometabolic diseases risk factors.
- Inter-individual variability of insulin in the response to flavanols was limited for insulin compared to other cardiometabolic biomarkers (1,2)
- This could be partly explained by 1) small number of trials reporting data for specific subgroups(e.g gender, medication use)
 2) broad range of doses and duration tested among the studies.

Reference

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Figure A

-2.00 -1.00 0.00 1.00 Farours Flavanol Farours Contro

Study name	Sample size		Time	Statisti	Statistics for each study			SDM and 95% CI					
т	reated	Control	point (weeks)	SDM	95% CI p-Value				Relative weight				
Brown 2011	63	65	6	-0.054	-0.401	0.292	0.759	- I		- C		- I	6.19
Kovacs 2004, a	51	53	13	-0.176	-0.561	0.209	0.371						5.01
Kovacs 2004, b	51	53	13	-0.184	-0.569	0.202	0.351		– I –				5.01
Akazome 2010	43	44	12	-0.179	-0.600	0.242	0.405						4.19
Mielgo-Avuso 2014	40	43	12	-0.019	-0.450	0.411	0.931						4.01
Mirzaei 2009	36	46	8	-0.092	-0.529	0.344	0.679			O			3 90
Hsu 2008	41	37	12	-0.158	-0.603	0.287	0.487		– I –				3.75
Chen 2015	39	38	12	-0.010	-0.456	0.437	0.967			ţ			3.73
Lin 2014	39	38	16	-0 144	-0.592	0.303	0.527		- I -				3 72
Bohn 2014 b	38	39	26	-0.165	-0.613	0.282	0.469		I –				3 71
Bohn 2014 a	38	39	26	-0.235	-0.684	0.213	0 304		I –	-0-			3 70
Wu 2012 a	37	32	8	-0.249	-0 724	0.226	0 304		I —	-0-			3 30
Hsu 2011	35	33	16	-0.205	-0.681	0.272	0.400		I –				3 27
Wu 2012 h	34	32	8	-0.280	-0.765	0.205	0.258						3.16
Rostami 2015	32	28	8	_0.200	-0.803	0.217	0.250						2.86
R101 2006	24	31	1	0.074	0.607	0.460	0.200		–	d			2.60
Bogdanelci 2012	24	28	13	0.610	1 1 5 5	0.400	0.024						2.02
Nickols Richardson 201	1 26	25	19	-0.019	0.5/0	0.540	1.000			<u>_</u>	-		2.33
Almooranti 2012 a	20	21	10	0.000	0.728	0.193	0.601				.		2.47
Nagao 2000	22	20	12	0.729	1 2 4 7	0.405	0.021						2.03
Hursel 2009	20	20	12	-0.728	-1.54/	-0.109	0.629						1.94
Hursel 2009, a	20	20	13	0.231	0.952	0.407	0.025						1.95
Desideri 2009, 0	20	20	0	-0.231	1 010	0.391	0.400						1.92
Almony 2012, 0	21	21	0	-0.393	-1.018	0.252	0.218			-			1.90
Essor 2014	10	20	4	-0.795	-1.421	-0.105	0.015						1.00
Desideri 2012 a	20	15	÷	-0.215	1 225	0.020	0.063			_			1.00
Mastariana 2015	20	1.1	0	-0.003	1 204	0.029	0.002						1.80
Standall Hallis 2010	29	14	36	-0.041	-1.294	0.011	0.034						1.75
Mastariana 2015	23	10	20	-0.091	-1.346	-0.055	0.039						1.75
Mastolacovo 2013, 6	17	14	0	-0.799	-1.439	-0.140	0.018		-				1./1
Nagao 2005	17	18	12	-0.279	-0.945	0.58/	0.412			<u> </u>			1.08
Fukino 2008, 6	13	15	8	-0.182	-0.899	0.330	0.620						1.45
Fukino 2008, a	14	10	8	-0.294	-1.015	0.427	0.425				_		1.45
Gutierrez-Saimean 2010	20	10	4	-0.078	-0.85/	0.081	0.840				_		1.29
Davison 2008	12		12	-0.984	-1.800	-0.118	0.026						0.99
Muniyappa 2008	10	9	2	-0.233	-1.119	0.048	0.602				_		0.95
Grassi 2005	10	10	2	-0.010	-1.515	0.281	0.179				_		0.92
Dower 2015	9	8	4	-0.296	-1.203	0.662	0.545			<u> </u>			0.81
Ravn-Haren 2013, d	0	0	4	-0.126	-1.209	1.007	0.827						0.58
Kavn-Haren 2013, c	0	0	4	-0.248	-1.383	0.888	0.669						0.58
Mellor 2010	0	0	8	-0.398	-1.540	0.745	0.495						0.57
Ravn-Haren 2013, a	6	6	4	-0.502	-1.652	0.647	0.392				-		0.56
Kavn-Haren 2013, b	С	С	4	-0.015	-1.254	1.225	0.981						0.48
Random overal	leffeo	t		-0.248	-0.334	-0.162	0.000	2.00	1.00	- 0.00	1.00	2.00	
Eiguro B								-2.00	-1.00	0.00	1.00	2.00	

Figure 1A & B: Forest plot of the effect of flavanol-containing products on HOMA_IR (A) and insulin (B) SDM: standardised mean difference, CI: confidence interval

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